Ureido Derivatives Of Poly-4-Amino-2-Carboxy-1-Methyl Pyrrole Compounds For Treatment Of inflammation

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Serial No. 60/067,526 filed Dec 4, 1997

Inflammatory reactions arising from a variety of medical conditions may have serious medical consequences when poorly controlled. Such inflammatory reactions contribute to a variety of disease states such as arthritis, asthma, non-bacterial medicated respiratory distress syndrome, reperfusion injury, and blunt force trauma. Accordingly, there is a need for new methods of diminished inflammation, especially acute inflammation.

This invention describes a method of inhibiting inflammation, particularly non-TNF dependent inflammation, by administering pharmacologically active ureido derivatives of distamycin. Since TNF is only one of many inducers of chemokines, this invention provides a more inclusive method for treatment of many inflammatory conditions, including conditions in which TNF does not play a substantial deleterious role in the pathology of the condition.

Therapeutic Chemokine Antagonists

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DHHS Reference No. E–170–96/0 filed Sep 06, 1996; PVT/US97/15594 filed Sep 05, 1997

This invention relates to a new class of chemoattractant antagonists, which are therapeutic candidates for treating disease conditions involving recruitment of inflammatory cells. These chemoattractant antagonists are comprised of a group consisting of gp120, gp41, domains and variants of gp41 and gp120.

Chemoattractants include the subgroup of chemokines and are known to mediate chemotaxis and other pro-inflammatory phenomena. The chemoattractants are generally short peptides. The family of chemokines is subdivided into distinct subfamilies, C–X–C and C–C, based on the arrangements of the first two cysteines of the primary amino acid sequence.

Members of the chemokine subfamily have remarkable similarities in their structural organization and biochemical properties. These homologies are consistent with the similarities observed in their biological effects, both in vitro and in vivo. These properties have prompted speculation that chemokines are mediators in autoimmune and allergic disorders.

Dated: November 16, 1998.

Jack Spiegel,

Director, Division of Technology Development and Transfer, Office of Technology Transfer.

[FR Doc. 98–31730 Filed 11–27–98; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing: Drug and Method for the Therapeutic Treatment of Primary Brain Tumors (Such as Intracranial Human Glioma, Astrocytomas, Medulloblastomas and Metastatic Tumors to the Central Nervous System)

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice.

SUMMARY: The National Institutes of Health (NIH) is seeking Licensees to further develop, evaluate, and commercialize a Transforming Growth Factor-alpha-Pseudomonas Exotoxin fusion protein, known a TGF-alpha-PE38, for the therapeutic treatment of refractory brain tumors such as intracranial human glioma, astrocytomas, medulloblastomas and metastatic tumors to the central nervous system (''SNS'').

The invention claimed in USPN 4,892,827, Entitled: ''Recombinant Pseudomonas Exotoxins: Construction of an Active Immunotoxin with Low Side Effects,'' is available for licensing on an exclusive or non-exclusive basis (in accordance with 35 USC 207 and 37 CFR part 404) with the Field of Use limited to the therapy of primary brain tumors, metastatic carcinomas, and leptomeningeal carcinomatosis.

ADDRESSES: Licensing information and copies of the U.S. patent referenced above may be obtained by contacting J.R. Dixon, Ph.D., Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7056 ext. 206; fax: 301/402–0220; e-mail: ''DixonJ@od.nih.gov''. Respondees interested in licensing the invention will be required to submit an ''Application for License to Public Health Service Inventions.''

SUPPLEMENTARY INFORMATION: Epidermal growth factor receptor (''EGFR'') is amplified or over expressed in many malignant gliomas, other primary brain tumors, and carcinomas of epithelial origin (e.g., breast, lung, etc.) but is low or undetectable in normal brain tissue. TGF-alpha-PE38 represents a growing class of recombinant toxins designed for use in targeted cancer therapy. These genetically engineered chimeric proteins consist of a targeting moiety and a cytotoxic moiety. While TGF-alpha-PE38 is extremely toxic to tumor cells that have a relatively high expression of EGFR, it is also active against primary human brain tumor cells which are known to have moderate to high EGFR expression. Direct delivery of TGF-alpha-PE38 into brain tumors by intratumoral implanted catheters or controlled-release biodegradable polymers or intrathecal administration into the cerebrospinal fluid of patients with leptomeningeal carcinomatosis, may represent clinically useful applications of recombinant toxin therapy in tumors with high EGFR expression.

Anaplastic astrocytoma and glioblastoma, the most common primary brain tumors in adults, respond poorly to all current therapies: Median survival for patients with these tumors ranges from 19 to 57 weeks. Local tumor recurrence also constitutes a significant problem in medulloblastoma, the most common childhood brain tumor. Despite 5-year survivals for medulloblastoma exceeding 80% in some studies, nearly half of these patients will eventually die from progressive tumor. Treatment failure in patients with brain tumors is a multifactorial process involving the intrinsic resistance of these tumors to radiation therapy and chemotherapy, the development of acquired treatment resistance, and limitations of drug delivery due to blood-brain barrier restrictions. Local recurrence of brain tumors represents the most common pattern of treatment failure. Accordingly, the identification of new therapeutic agents that have high intrinsic activity against brain tumors and are appropriate for local therapy remains a major goal of the NIH.

Dated: November 16, 1998.

Jack Spiegel,

Director, Division of Technology Development and Transfer, Office of Technology Transfer.

[FR Doc. 98–31731 Filed 11–27–98; 8:45 am]

BILLING CODE 4140–01–M